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Long-Term Follow-Up of Tandem High-Dose Therapy with Autologous Stem Cell Support for Adults with High-Risk Age-Adjusted International Prognostic Index Aggressive non-Hodgkin Lymphomas: A GOELAMS Pilot Study

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Single high-dose therapy (HDT) followed by autologous peripheral blood stem cell (PBSC) support improves complete response and overall survival (OS) in untreated aggressive non-Hodgkin's lymphoma (NHL). However, patients with a high age-adjusted international prognostic index (aa-IPI equal to 3) still have poor clinical outcome despite high dose intensity regimen. To improve complete response in this subgroup, the French Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) conducted a pilot phase II trial (073) evaluating tandem HDT with PBSC support in a series of 45 patients with aa-IPI equal to 3 untreated aggressive non-Hodgkin's lymphoma. After induction with an anthracyclin-containing regimen, responders underwent tandem HDT conditioned by high-dose mitoxantrone plus cytarabine for the first HDT and total-body irradiation (TBI), carmustine, etoposide, and cyclophosphamide for the second HDT. Thirty-one patients out of 41 evaluable patients completed the program. There were 4 toxic deaths. The complete response rate was 49%. With a median follow-up of 114 months for surviving patients, the OS was 51%, and 19 out of the 22 patients (86%) who reached a complete response are alive and relapse-free. Recent prospective evaluation of quality of life and comorbidities of surviving patients does not reveal long-term toxicities of the procedure. In the era of monoclonal antibodies and response-adapted therapy, the role of tandem HDT still need to be determined.

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INTRODUCTION

In 1993, the age-adjusted International Prognostic Index (aa-IPI) was set up to predict survival of patients under 60 years of age with aggressive non-Hodgkin's lymphoma (NHL) treated with conventional anthracyclin-containing regimens [1]. Based on 3 factors (lactate dehydrogenase, Ann Arbor staging, and performance status), 4 prognostic groups were defined: low, low intermediate, high intermediate, and high. In the latter group, after CHOP-like regimens, the complete response (CR) and 5-year overall survival (OS) rates were

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46% and 32%, respectively. Improved CR and OS have been described with single high-dose therapy (HDT) followed by autologous peripheral blood stem cell (PBSC) support in first-line treatment of aggressive NHL, but high-risk patients still have a poor prognosis [2,3]. In an attempt to improve the outcome of these patients, before the era of monoclonal antibodies, the French Groupe Ouest-Est des Leucémies et Autres Maladies du Sang (GOELAMS) conducted the 073 study to evaluate upfront tandem HDT with PBSC support in aggressive NHL patients with high aa-IPI.

DESIGN AND METHODS

Inclusion Criteria

This phase II multicenter study enrolled patients aged from 15 to 60 years with previously untreated histologically proven aggressive NHL: F, G, H according to the Working Formulation [4] (WHO classification was not published when the study was designed), a high aa-IPI (equal to 3), proper underlying organ function, and absence of HIV infection. Patients with transformed low-grade, lymphoblastic, mantle-cell, or Burkitt's lymphoma were excluded. The trial was approved by the Ethics Committee of the Region Pays de la Loire, France, on 01/09/1994. All patients provided written informed consent.

Treatment

Two courses of the CEEP regimen were planned with cyclophosphamide 1200 mg/m^2, epirubicin 100 mg/m^2, vindesine 3 mg/m^2 intravenously on day 1 and prednisone 80 mg/m^2 orally or intravenously from days 1 to 5, at 2-week intervals. Granulocyte colony-stimulating growth factor (filgrastim, Amgen, Neuilly-sur-Seine, France) was administrated at the dose of 5 μg/kg/day from day 6 of each course of CEEP, until apheresis procedures were completed. Intrathecal injections of 15 mg methotrexate and 20 mg methylprednisolone were routinely given on the second day of each CEEP course.

The first HDT (HDT1) was planned on day 36. The conditioning regimen was mitoxantrone 45 mg/m^2 intravenously on day 1 and cytarabine 1000 mg/m^2 by a 3-hour infusion every 12 hours from days 1 to 4. Patients were eligible for the second HDT (HDT2) if they reached at least a partial response (PR) after HDT1. The conditioning regimen of HDT 2 started from day 30 to day 45 after the first stem cell infusion, and consisted of 1200 cGy total-body irradiation (TBI) in 6 twice-daily 200 cGy fractionated doses with a 800 cGy pulmonary shielding, followed by CBV: carmustine 300 mg/m^2 intravenously on day 4, and etoposide 200 mg/m^2 and cyclophosphamide 1500 mg/m^2 intravenously from days 5 to 8. For each HDT, at least 2×10^6/kg CD34$^+$ unpurged PBSC were infused the day following the last chemotherapy, and 5 μg/kg/day filgrastim was started on the same day. Because 3 patients out of 16 patients who had received HDT2 experienced lethal toxicity, the intensity of the TBI-containing regimen was reduced to TBI (same schedule) + cyclophosphamide (60 mg/kg for 2 days).

Staging and Assessments

Patients were staged at diagnosis by clinical examination, CT scan, and bone marrow (BM) biopsy. Diagnostic slides were reviewed centrally by 1 pathologist (A.M.). The evaluation responses by CT scan were planned after HDT1 and HDT2.

Response Assessments

The standardization of response evaluations for lymphoma was not published at the time of study design [5]. CR was defined by the disappearance of all documented disease. Additionally, patients with persistent CT abnormalities but reduction of at least 75% in the largest diameter of all measurable lesions without the persistence of BM involvement were deemed to be in CR. PR was defined by a reduction of at least 50% in the largest diameter of every measurable lesion, even if BM involvement persisted. Treatment was considered to have failed if patients experienced disease progression before the end of the treatment program.

Follow-Up

Patients were monitored by physical examination every 3 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter. CT scans were performed every 6 months during the first 2 years and then at the discretion of the treating physician. As a part of this long-term evaluation of the procedure, survivors were assessed for health-related quality of life (HRQoL) and comorbidities with the EORTC QLQ-30, version 2 [6] and the Self-Administered Comorbidity Questionnaire (SCQ) [7], respectively.

Statistical Analysis

The primary endpoint was the CR rate. With a hypothesis of improving the CR rate from 46% [1] to 60%, more than 40 patients had to be included to ensure that the lower limit of the 95% confidence interval (CI) around 60% will be >40%. Thus, this pilot study was planned to include 45 patients with an interim analysis after the first 20 inclusions. Secondary endpoints were the overall response (OR), OS, progression-free survival (PFS) rates, and toxicity. OR was defined as the addition of CR and PR; OS was measured from the time of inclusion to death from any cause or the date of last contact; PFS was measured from the time of inclusion to relapse or death in remission. OS and PFS rates were calculated according to the Kaplan-Meier method.

The log-rank test was used to compare the survival curves between groups. Univariate analysis and multivariate analysis were performed with the use of the Cox model. Variables with a *P* value lower than 0.25 in the univariate analysis were retained for the multivariate analysis. The Cox regression gave hazard ratio (HR). The type I error was set to 5%. Statistical analysis was performed with the R software version 2.7.2. All parameters were evaluated on an intent-to-treat basis.

RESULTS

We report on the results of tandem HDT in a specifically adverse prognostic population of aggressive NHL patients.

Description of Patients and Treatment Outcome

Between October 1994 and July 1999, 45 patients were included in 10 GOELAMS centers. Four patients were excluded from the analysis because of inclusion criteria violations (aa-IPI <3 for all). Characteristics of the 41 patients at inclusion are summarized in Table 1. A total of 31 patients (76%) completed the whole procedure. The 10 others experienced early progression (n = 5), toxic death (n = 1), protocol violations (n = 3), and hepatitis B reactivation after HDT1 (n = 1). A total of 4 toxic deaths occurred during treatment: bacterial septicemia after the first CEEP (n = 1), and after HDT2 in 3 cases (septic shock, interstitial pneumonitis, and hemorrhagic shock). HDT2 conditioning was subsequently reduced, resulting in the absence of additional lethal toxicity (Figure 1). All patients mobilized correctly with a median of 2 aphereses (required PBSC dose/kg = 4×10^6 $CD34^+$). Hematologic toxicity was acceptable, with a median duration of neutropenia (neutrophil count $<0.5 \times 10^9$/L) of 9 and 11 days following HDT1 and HDT2, respectively.

Table 1. Characteristics of the 41 Patients

	N	(%)
Sex		
Female	19	(46)
Male	22	(54)
Histologic subtype		
Diffuse mixed small and large cell (F)	1	(2)
Diffuse large cell (G)	31	(76)
Large cell immunoblastic (H)	3	(7)
Ki-1 positive anaplastic	1	(2)
Peripheral T cell	2	(6)
Other	3	(7)
Presence of B symptoms	32	(78)
Performance status		
2	17	(41)
3	22	(54)
4	2	(5)
Ann Arbor stage		
III	4	(10)
IV	37	(90)
Nodal involvement ≥4	16	(39)
Extranodal involvement ≥2	23	(56)
Bulky disease (≥10 cm)		
Abdominal	7	(17)
Thoracic	2	(6)
Serous effusion	18	(44)
Marrow involvement	15	(37)

N indicates number of patients.

Response and Survival Analysis

Eighteen patients (40%) experienced a CR after HDT1 and 22 patients (49%) after HDT2. OR was achieved for 32 patients (71%) after HDT1 and for 26 patients (58%) after HDT2. With a median follow-up time of 114 months (range: 23-159), 10-year OS and PFS are estimated by 51% (95% confidence interval [CI] 38%-69%) and 53% (95% CI 38%-73%), respectively (Figure 2).

All patients who survived after 10 months, except 1, were relapse-free to date. The patient who relapsed with a nonaggressive histology (follicular) was successfully treated using rituximab alone. The occurrence of a plateau after 10 months suggests that a subgroup of aa-IPI equal to 3 patients with aggressive NHL might be cured by tandem autologous HDT.

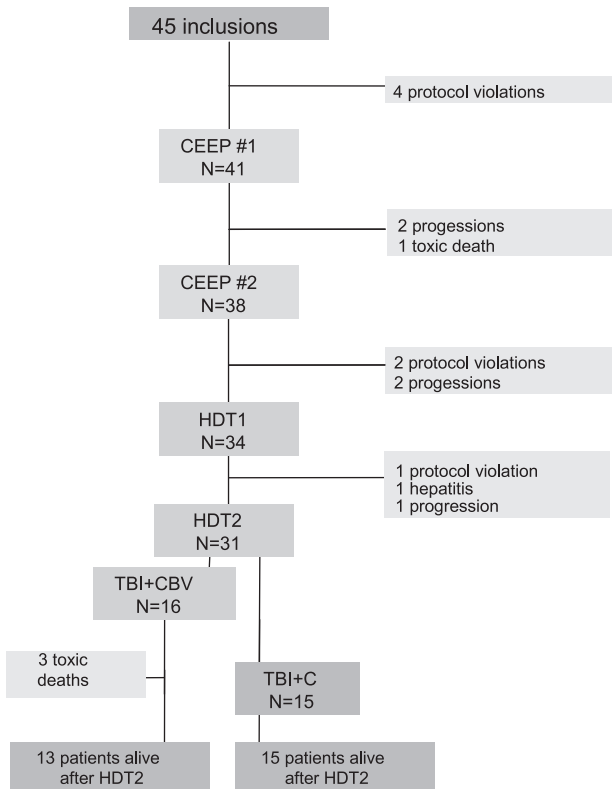

Figure 1. Flowchart of the patients included in the GOELAMS 073 trial. C indicates cyclophosphamide; CBV, carmustine, etoposide, and cyclophosphamide; CEEP, cyclophosphamide, epirubicin, vindesine, and prednisone; HDT, high-dose therapy; N, number of patients; PBSC, peripheral blood stem cell; TBI, total-body irradiation.

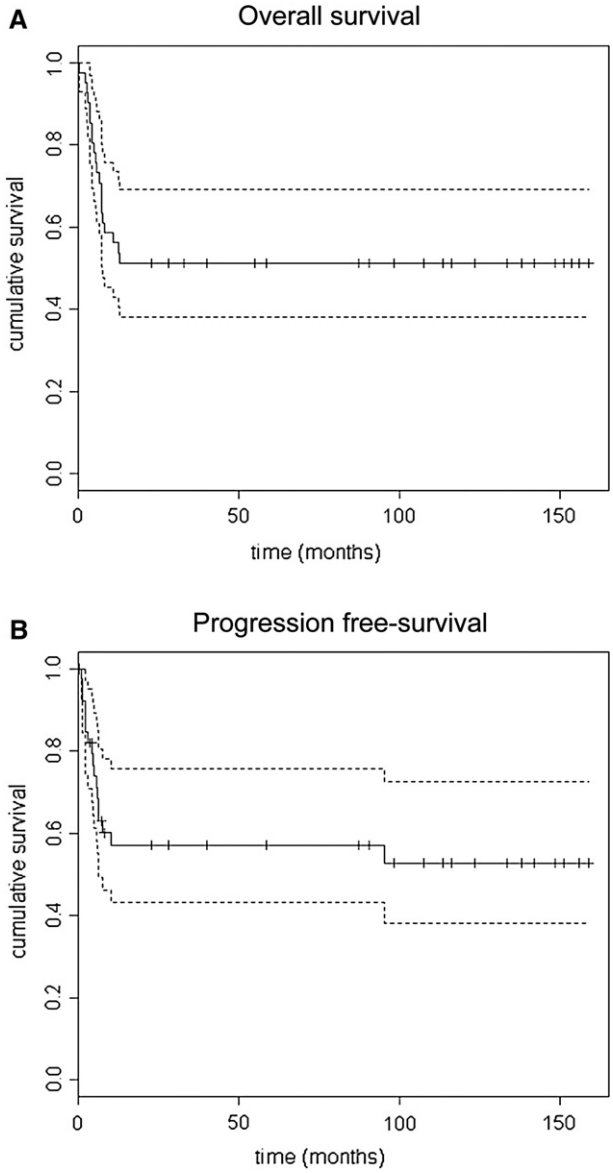

Figure 2. Patient outcomes. (A) OS. (B) PFS.

Site of Relapse

Fifteen patients experienced progressive disease or relapse after completion of the whole procedure. Among the 9 patients for which relapse site information was available, 8 (89%) relapsed at the initial disease site. One patient, who had a history of brain disease at enrollment, experienced relapse in the central nervous system.

Prognostic Factors

In a univariate analysis, OS was negatively affected by serous effusion ($P = .042$), and a favorable prognosis of the G and H histology subtypes ($P = .014$) was observed. PFS was affected by histology ($P = .004$) only. On multivariate analysis, G and H histology subtypes and serous effusion remained statistically significant (HR: 3.9, 95% CI: 1.17%-12.91% and HR: 2.9, 95% CI: 1.04%-8.68%, respectively) for OS, G and H histologies (HR: 8.5, 95% CI: 1.83%-39.47%) for PFS.

Long-Term Toxicity

Three nonfatal secondary malignancies have occurred: 1 adenoid cystic carcinoma treated by surgery and 2 breast cancer treated with radiochemotherapy or with surgery. Of note, no myelodysplastic syndrome or secondary acute myeloblastic leukemia had occurred to date.

Quality of Life and Medical Late Effects

Twenty-three patients were eligible for the long-term HRQoL questionnaire and SCQ. Of these, 5 were lost to follow-up and 6 either actively or passively declined participation.

For the EORTC QLQ-30 functioning scales, 82% of patients scored 50 or above, representing good quality of life, on the global health status scale, and no patients scored 50 or below on the physical functioning scale. Only a small proportion of patients had scores

Table 2. Summary Statistics of HRQoL Functional and Symptoms Scales

	All patients
Physical functioning	
Median score (95% CI)	86 (53-100)
Mean score (IQR)	90 (87-93)
n <50	0
% <50	0
Role functioning	
Median score (95% CI)	85 (33-100)
Mean score (IQR)	92 (83-100)
n <50	1
% <50	8%
Emotional functioning	
Median score (95% CI)	74 (8-100)
Mean score (IQR)	79 (75-83)
n <50	2
% <50	16%
Cognitive functioning	
Median score (95% CI)	79 (33-100)
Mean score (IQR)	92 (83-100)
n <50	2
% <50	16%
Social functioning	
Median score (95% CI)	74 (17-100)
Mean score (IQR)	67 (50-83)
n <50	1
% <50	8%
Fatigue	
Median score (95% CI)	32 (0-78)
Mean score (IQR)	33 (22-44)
n <50	2
% <50	16%
Global quality of life	
Median score (95% CI)	68 (0-100)
Mean score (IQR)	71 (67-75)
n <50	1
% <50	8%

IQR, Indicates interquatile range; N, number of patients; CI, confidence interval.

Table 3. Frequency and Percentage of Selected Self-Reported Late Effects

Late effects	n	(%)
Number	8	(67)
Cardiopulmonary impairments	4	(33)
Hypertension	2	(17)
Dyspnea	3	(25)
Neuromotor impairments	3	(25)
Tremor, weakness or balance	3	(25)
Psychiatric disorders	3	(25)
Depressive syndrome	2	(17)
Bipolar affective disorder	1	(8)
Endocrine impairments	2	(17)
Sterility	1	(8)
Diabetes	1	(8)
Neurosensory impairments	2	(17)
Vertigo	1	(8)
Tinnitus or ringing in the ears	1	(8)
Eye impairments	2	(17)
Cataracts	2	(17)
Hematologic impairments	2	(17)
Anemia	2	(17)
Exocrine impairments	1	(8)
Pancreatic insufficiency	1	(8)
Bone impairments	1	(8)
Osteoporosis	1	(8)
Renal impairments	1	(8)
Chronic renal failure	1	(8)

n indicates number of patients.

of 50 or below on the role, emotional, cognitive, and social functioning scales (8% to 16%). For the symptom scales, 16% of patients scored over 50 on the fatigue scale, which thus represents the most common symptom (Table 2).

The prevalence of selected medical late effects in long-term survivors is listed in Table 3. Among patients who responded to the SCQ questionnaire, the following conditions were reported: 3 breathing problems, 5 neuromotor and/or neurosensory impairments, 2 major depressions, 1 bipolar affective disorder, 1 infertility, 2 cataracts, 1 pancreatic insufficiency, 1 osteoporosis, and 1 chronic renal failure.

DISCUSSION

Other studies evaluating upfront tandem HDT in the setting of aa-IPI 1 to 3 aggressive NHL reported CR rates between 50% and 92% and 3-year OS rates between 41% and 84% [8-10]. To the best of our knowledge, this study is the first to evaluate tandem HDT in the specific setting of untreated high-risk aggressive NHL (aa-IPI equal to 3). With a CR rate of 49% and a 10-year OS estimate of 51%, the 073 trial compares favorably with other studies.

As in other tandem HDT studies, in this high-risk population of patients, an intensified induction regimen by CEEP was chosen. The use of this not standard and generally more intensive treatment might have positively affected relapse and survival rates. An other important prognostic factor in this subgroup is the quality of remission before HDT. Unfortunately, in this study, the disease status before the first HDT was not evaluated, and consequently cannot be used as prognostic factor.

The toxicity of this tandem HDT procedure partially impaired the results in terms of OS. In other tandem HDT studies, improved results were obtained using non-TBI myeloablative regimens [8-10]. However, our results are not inferior to those published in frontline single HDT [11-13] and raise the question of the role of TBI, as previously discussed in other studies [14,15].

In this study, we examined long-term quality of life among surviving patients. Scores are similar (mean difference <10 points) [16] to those of long-term survivors of Hodgkin lymphoma [17,18]. Most survivors of aggressive NHL enjoyed normal life after tandem HDT.

Whether a high aa-IPI score was an appropriate definition of a poor-risk patient population is questionable, because other prognostic factors have been identified, such as bulky disease [19], β-2 microglobulin [20], genomic profiling [21,22], and failure to achieve complete response in the era of positon emission tomography evaluation [23]. Alternatively to performing tandem autologous transplantation, chemotherapy may be intensified. However, the role of this approach has not yet been demonstrated in poor-risk aggressive NHL [24].

Addition of rituximab to standard chemotherapy has shown to improve outcome in older patients with aggressive NHL. Rituximab, in addition to single HDT in untreated aggressive NHL, improved CR and PFS. however with mixed aa-IPI [25,26]. Rituximab-containing induction chemotherapy followed by a single transplant is currently being compared to standard immunochemotherapy as first-line treatment by the GOELAMS group. The question about the clinical benefit of adding rituximab to tandem HDT remains unanswered.

In the absence of randomized trials, the clinical benefit of tandem HDT still needs to be determined in the worst prognostic group of patients with aggressive NHL.

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AUTHORSHIP STATEMENT

H.M. and E.G. collected the data, analyzed the data, and wrote the paper. E.D. and N.M. designed the research, collected the data, analyzed the data,

and wrote the paper. E.P. performed the statistical analysis. V.D., S.F., C.B., and N.M. recruited patients and collected the data. H.M., T.G., S.F. and E.G. performed the long-term follow-up. A.M. performed the central pathology review. N.M. was the principal investigator. All authors reviewed the final version of the manuscript. The authors report no potential conflict of interest.

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APPENDIX

Members of the GOELAMS study group who contributed to patient's accrual. Pr. Noël Milpied, Nantes (12); Dr. Vincent Delwail, Poitiers (8); Dr. Sylvie François, Angers (4); Martine Escoffre-Barbe, Brest (3); Dr. Christine Le Maignan, Paris (3); Luc Sensebé, Brest (3); Stéphane Le Tortorec, Nantes (2); Philippe Colombat, Tours (2); Dr. Eric Deconinck, Besançon (2); Dr. Claude-Eric Bulabois, Besançon (1); Dr. Philippe Casassus, Bobigny (1); Dr. Jacqueline Dugay, Le Mans (1); Dr. Martine Gardembas, Angers (1); Dr Hervé Maisonneuve, Nantes (1); Dr Philippe Moreau, Nantes (1).

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